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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/829,513	WOLFF ET AL.	
	Examiner	Art Unit	
	Maria Leavitt	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAIL ACTION

Claims 1-13 are cancelled by Applicant's amendment dated 06/08/2004.

Claims 14-26 are pending to which the following grounds of rejection are applicable.

Claim Rejections - 35 USC § 112 – written description

Claim 14-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to any person skilled in the art to which it pertains, or with which it is most nearly connected, at the time the application was filed, that the inventor, at the time the application was filed, had possession of the claimed invention.

Claims 14-26, when given the broadest reasonable interpretation encompass a genus of unspecified chelators, which not only must exhibit the ability to electrostatically complex a nucleic acid but also to carry the nucleic acid across the cell membrane to reach a target cell. Further, the complex can bind any polymer or molecule other that the nucleic acid to direct the complex to a cell location. The specification describes the term "chelator" as being any polydentate ligand, *e.g.,* a chemical compound or molecule that exhibits the ability to occupy more than one site in the coordination sphere of an ion (p. 10, lines 25-30). The invention embraces an extremely large number of possible compounds, which not only act as polydentate ligands but are also able to complex electrostatically with a nucleic acid and subsequently enhance the delivery of said nucleic acid across the cell membrane of a target cell. Additionally, Applicant invention claims generically an expressible polymer (p.12, lines 10-15).

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude that the inventor(s) had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention was "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention (January 5, 2001 Fed. Reg., Vol. 66, No. 4, pp. 1099-11). Moreover, MPEP 2163 states:

> [A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.

Overall, what these statements indicate is that the Applicant must provide adequate description of such core structure and function related to that core structure such that the Artisan could determine the desired effect. Hence, the analysis below demonstrates that Applicant has not determined the core structure for full scope of the claimed genera. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the invention embraces an extremely large number of possible compounds, which not only act as polydentate ligands but are also able to complex electrostatically with a nucleic acid and subsequently enhance the delivery of a nucleic acid across the cell membrane of a target cell. However,

the as-filed specification only provides sufficient description of chelator-polycationic polymer, which must exhibit the ability to electrostatically bind to an expressible nucleic acid polymer (e.g., crown ether containing polymers and polycation systems containing crown ether) for use within the context of the claimed invention, *e.g.,* enhance the delivery and expression of a desired nucleic acid. Moreover, Applicant invention claims generically an expressible polymer (p.12, lines 10-5). However, the as-filed specification only provides a description of one species of an expressible polymer as generically claimed, *e.g.,* an expressible nucleic acid. Applicant does not disclose other specific teachings of a number of other species of chelators that are attached to a polymer and then associated with another polymer other than DNA. Moreover, the specification does not provide any disclosure as to what would have been the required structure, which would cause any enhancement in the delivery of a nucleic acid across the cell membrane of a target cell. Furthermore, such increased expression of a transfected nucleic acid is not supported by the consistency of results as disclosed by Applicant, for example, in Example 16, intramuscular injection of DNA-Polyvinylbenzo-18-6 Complexes with increasing amounts of PV18C6, 0.085 and 0.17 μmol, only correspond with increased levels of luciferase transfection activity, 23839 and 5486 RLU respectively, at lower concentration of the pIlucDNA vector (p. 32, Table). Higher concentrations result in cythopatic effects. These results indicate the complex process of the polynucleotide condensation utilizing crown esters containing polymers or polycationic systems to efficiently deliver and express a polynucleotide across a cell membrane of a target cell.

Next then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e., enhance the delivery of a nucleic acid across the cell membrane of a target cell), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the no other characteristic in addition to the functional discussed above is disclosed. Such functional characteristics, however, do not allow one of skill in the art to distinguish the different members of the genera form each other.

Applicant's attention is directed to *In re Shokal*, 113 USPQ 283 (CCPA 1957), wherein it is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 CCPA (Patents) 1309, 97 F2d 623, 38 USPQ 189; *In re Wahlforss*, 28 CCPA (Patents) 867, 117 F2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

Hence what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structure(s) of component(s) that are linked structurally to the extent that the described structures with essential elements must be able to reflect any of the disclosed biological functions as contemplated by the as-filed specification. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which is not conventional in the art as of applicants effective filing date. It appears that only

nucleoside is and its making are conventional in the state of the prior art and are disclosed in the as-filed disclosure.

Hence, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claim Rejections - 35 USC § 112 – scope of enablemet

Claims 14-26, are rejected under 35 U.S.C. 112, first paragraph, because the specification is enabling only for claims limited to:

A process for delivering a polynucleotide to a cell comprising:

a) forming a complex consisting of a polynucleotide and a chelator, wherein electrostatic interaction of the chelator with one or more components of the complex requires the presence of a metal ion coordinated by the chelator; and

b) delivering the complex to the cell.

The specification does not reasonably provide enablement for claims directed for a process of delivering a polynucleotide to a cell comprising a complex consisting of, i) a polynucleotide and a primary amine-containing molecule, ii) adding a chelator to the complex to form a new complex and iii) delivering the new complex to the cell. The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to use the invention commensurate in scope with this claim.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claim

The present invention relates to a process of delivering nucleic acids, genes, molecules and polymers by using chelators and polychelators. The present invention when given the broadest reasonable interpretation is drawn to a process of delivering a polynucleotide to a cell wherein the delivery step encompasses not only the delivery of a chelator containing a polycation/nucleic acid polymer complex but also a nucleic acid by itself even when the step of associating the chelator to the nucleic acid polymer already has been carried out.

Applicant describes in 16 examples the steps of associating a complex of chelator-polycationic polymer, wherein the chelator (i.e., crown ether containing polymers and polycation systems containing crown ether), must exhibit the ability to associate with polyamines (e.g., polylysine, histone, polyethylenimine). Further, the polychelator can be put in contact with another polyion to compact the polymer. Additionally, the charged chelator or polychelator can be associated with a peptide, protein, signal or amphipathic compound for miscellar structures (p. 17, lines 29-31) to recharge, attach signals, increase stability and add protection (p.17, lines 5-9). Applicant teaches in examples 15 and 16 enhanced *in vitro* and *in vivo* transfection efficiency for crown ether containing polymers in relation to a control plasmid devoid of crown ether association at low concentration of complexes.

The detail of the disclosure provided by the Applicant, in view of the prior Art, must encompass a wide area of knowledge to enable one of ordinary skill in the art at the time of the invention to practice the invention without undue experimentation. However, as it will be discussed below this undue experimentation has not been overcame by the as-filed application.

Though the as-filed specification provides sufficient description of chelator-polycationic polymers, which must exhibit the ability to electrostatically bind to an expressible nucleic acid polymer (e.g., crown ether containing polymers and polycation systems containing crown ether) for use within the context of the claimed invention, *e.g.,* enhance the delivery and expression of a desired nucleic acid, the broad aspects of gene therapy to express a nucleic acid with any type of chelator polymeric complexes is not reasonably enable for the full scope embraced by the claim.

State of the prior art and the predictability or lack thereof in the art

The Invention is in the nature of the process of using chelator containing compounds that are utilized in the delivery of molecules, polymers, nucleic acids and genes to animal cells.

A search of prior Art does not disclose of a process for delivering a polymeric molecule having a net positive charge comprising another polymeric molecule having a net negative charge (e.g. an anionic polymer (DNA)-cationic polymer complex, p. 7, lines 23-24) additionally conjugated to crown ether, wherein ions are added to the mixture thereby forming condensed DNA to enhance DNA transfection.

Regarding the claimed invention drawn to the use of any type of chelator- polymeric complexes, applicant' claims as written encompass methods employing any other chelators other than crown ether (e.g., systems containing atoms other than carbon in the ring of a

heterocyclic compound). As such, transfection with any DNA-chelator complex cannot predictable result in enhanced DNA delivered to a cell.

Hence, it would require undue experimentation to one of ordinary skill in the Art to determine the process of associating an extremely large number of possible compounds which not only act as polydentate ligands but also are able to complex electrostatically with a nucleic acid and subsequently result in enhanced transfection efficiency.

Guidance in the Specification and working examples

The as-filed specification only provides sufficient guidance for the delivery step directed essentially to delivering the chelator/nucleic acid polymer complex to a cell (p. 5, lines 13-14), further comprising the addition of an ion to one chelator and/or polychelator already associated with the DNA (see, Fig. 1 and Fig. 2 and abstract).

Level of Skill in the Art

The relative skill of those in the art is considered to be relatively high at the time the invention was made.

Analysis of Quantity of Experimentation

Applicant describes in 16 examples the steps of associating a complex of chelator-polycationic polymer, wherein the chelator (i.e., crown ether containing polymers and polycation systems containing crown ether), must exhibit the ability to associate with polyamines (e.g., polylysine, histone, polyethylenimine). Further, Applicant teaches in examples 15 and 16 enhanced *in vitro* and *in vivo* transfection efficiency for crown ether

containing polymers at low concentration in relation to a control plasmid devoid of crown ether complexes.

As such, and to the extent that the claimed invention is drawn to the make and use of a process of delivering a polynucleotide to a cell wherein the delivery step encompasses not only the delivery of a chelator containing a polycation/nucleic acid polymer complex but also a nucleic acid by itself even when the step of associating the chelator to the nucleic acid polymer already has been carried out the as-filed Application does not provide enablement for the presently pending claims encompassing any and/or all structures other than those indicated in the enabling embodiments.

Due to the large quantity of experimentation necessary to generate the infinite number of derivative as recite in claims 14-26 and subsequent screening for selection of a process of associating an extremely large number of possible compounds which not only act as polydentate ligands but also are able to complex electrostatically with any nucleic acid and subsequently result in enhanced transfection efficiency, one skilled in the Art will have to perform extensive experimentation with each of these parameters to find the embodiments embraced by Applicant's claim, and as such, this experimentation would be considered undue.

Conclusion

In conclusion, the disclosed information from the as-filed application plus the state of the prior art is not deemed sufficient to reasonably convey to one of ordinary skill in the art that the Specification is reasonably enabling for the full breadth of the claim at the time the invention was made. Such is because of lack of predictability in the process of associating an extremely large number of possible compounds which not only act as polydentate ligands but also are able

to complex electrostatically with any nucleic acid and subsequently result in enhanced transfection efficiency. Because of lack of working examples, insufficient guidance and direction in the specification, the inherent unpredictability in the art, the state of the art and the nature of the invention, one of ordinary skill in the Art to would be required to perform a large amount of experimentation to make an/or use the invention claimed by the Applicant.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 14-26 are rejected under 35 U.S.C. 102(b) as being anticipated by the Kayyem *et al.*, (WO 96/11712, International filing date: 11 October 1995).

Kayyem teaches a process for delivery a polymeric molecule having a net positive charge comprising another polymeric molecule having a net negative charge (e.g. an anionic polymer (DNA)-cationic polymer complex, p. 7, lines 23-24) conjugated to a plurality of targeting

moieties or physiological agents (p. 12, lines 1-3), including chelators bound to a contrast agents (page 10, paragraph 3; page 11, paragraph 2, pages 12 and 13, and pages 26-32) and therapeutic agents (p. 8, lines 23-26). Kayyem teaches that a plurality of chelators can be added to the -NH2 groups of the lysine side chains as linkers for binding to a plurality of contrast agents (page 10, paragraph 3), and that a chelator can be conjugated to any of the disclosed polymeric molecule (page 12). Cell targeting moieties and physiological agents, including contrast agents and therapeutic agents, are attached to one or both of the polymeric molecules (abstract). Furthermore, the abstract clearly states:

> "The delivery vehicles can be used in clinical protocols in which nucleic acids for gene therapy (expressible nucleic acids) and agents for MRI contrast are co-transported to specific cells allowing medical imaging monitoring of nucleic acid delivery" (see also p. 4, lines 16-22; and p. 14, 24-29). Moreover "the method comprises contacting the cell with a delivery vehicle of the invention and detecting the presence of the physiological agent (p. 5, lines 17-18)".

Additionally, on page 5, Kayyem discloses "In another embodiment, one of the polymeric molecules compris a nucleic acid which is complexed (electrostatically) with one or more polymeric molecules comprising a polyamine.

With respect to the limitation of recharging the polychelator to change the net charge and the limitation of an expressible nucleic acid being a first polyanionic polymer or molecule, Kayyem teaches the same on pages 7 and 8. More specifically, Kayyem states:

> "The delivery vehicles of the present invention comprise a fist polymeric molecule [expressible nucleic acid] and a second polymeric molecule [polycationic molecule, a complex composed of polylysine and a chelator, see page 10]. As indicated in Figure 1A, the delivery vehicle (1) comprises a first polymeric molecule (2) having an overall net

positive or negative charge which is employed as a scaffold to which an oppositely charged second polymeric molecule (3) is complexed. As shown in Figure 1B, some delivery vehicles include a third polymeric molecule (6) having a net charge opposite that of the first polymeric molecule and complexed with the first polymeric molecule. Preferably the first and second polymeric molecules are held together by electrostatic interactions and thus do not need to be covalently linked to each other. In certain embodiments, both the first and second polymeric molecules contain a mixture of charged groups and thus are zwitterionic. The depiction of linear polymeric molecules in Figure 1 is for illustrative purposes and is not necessarily preferred, as circular polymers such as plasmids [expressible nucleic acids] may also be used. The delivery vehicle will be in any configuration that is suitable for cellular uptake" (p. 7, lines 9-22).

In a preferred embodiment, the nucleic acid is double stranded, most preferably a double stranded plasmid (page 8).

Thus, Kayyem does teach that the second polymeric molecule can be recharged by preparing the molecule so as to contain a mixture of charged groups and/or by complexing a third polymeric molecule to the nucleic acid polymer.

In relation to the expressible plasmid, Kayyem states on page 8, lines 11-13:

"In one embodiment, the nucleic acid encodes a reporter gene, such that the uptake of the delivery vehicle can be additionally monitored by the presence or absence of the reporter gene and/or the protein encoded by the gene [protein expressed by the nucleic acid]."

More specifically, Kayyem teaches on page 8 through page 9 the use of the delivery vehicle to deliver and express a therapeutic protein encoded by a nucleic acid.

Further, as to the second polymeric molecule being a modified polysine composed of lysine/chelator based monomers linked by a covalent bond, Kayyem teaches on page 10, lines 20-26:

> "When polylysine is used as the second polymeric molecule, the –NH2 group of the lysine side chains at high pH serve as strong nucleophiles for multiple attachment of activated chelating agents. The invention takes advantage of both the polycationic and polynucleophilic nature of polyamines such as polysine. At high pH the lysine monomers are coupled to the physiological agents under conditions that yield on average 5-20% monomer substitutions. At physiological pH to low pH, the remaining unlabeled positively charged lysines facilitate nucleic acid bindings."

As to the linkage of a chelator to any of the cell targeting signals and/or physiological agents, Kayyem states on page 11, lines 10-13:

> "The cell targeting moieties and physiological agents described below are attracted to either polymeric molecule, although in a preferred embodiment they are both attached to the polycation".

By the term "physiological agent" herein is meant compounds which are desirable to deliver in a cell-specific manner.

In addition to particularly pointing out that the invention is not directed *per se* to just the delivery of contrast agents such as paramagnetic or superparamagnetic metals, Kayyem states clearly on the first paragraph of page 12, that the term "physiological agent" encompasses both contrast and therapeutic agents.

Kayyem also recognizes the toxicity of the use of some paramagnetic or superparamagnetic metals as contrast agents, and further provide a solution to the problem by teaching on page 12:

> "Gd(III) ions are extremely toxic to cells and therefore must be bound to a chelating agent which is then conjugated to the polymeric molecule [a second polymeric molecule,

for example]".

A number of chelating agents is further taught by Kayyem as being disclosed in a number of US patents cited on page 12 and expressly incorporated by reference.

In addition, Kayyem discloses on page 26 that pharmaceutically acceptable carriers including a salt [e.g., sodium carbonate] are employed in the preparation of a conjugate of chelators and a cationic polymer.

Absent evidence to the contrary, the delivery process and the compositions or conjugates disclosed in Kayyem have all of the properties cited in the claims, and to the extent that any minor modification such as the types of bonding and/or an incorporation of more charges to augment positive charges to enhance the delivery of nucleic acid into target cells, it would have been obvious for one of ordinary skill in the art to have modified such changes as long as such modifications are within the teaching of Kayyem' references to provide a synergistic effect in enhancing the delivery of the nucleic acid into a target cell for expression.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 14-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kayyem *et al.* taken with Hnatowich *et al.* (US Pat No. 5,980,861).

The teachings of Kayyem's reference are outline above.

Kayyem does not teach explicitly the use of crown ether associated with a plurality of crown ether chelators.

Hnatowich teaches that it is routine in the art at the time the invention was made to employ known chelators including crown ether, for conjugation to a polymer either by covalent or ionic bonding for the purpose of real time monitoring of the delivery of polymers including DNA (entire document, especially columns 11 and 12). In addition, Hnatowich teaches that crown ether chelators can be covalently bound to the anionic polymer (DNA) through the nitrogen atom that is provided on the nucleic acid, or through other functional moieties bound to the anionic polymer (column 12). More specifically, Hnatowich *et al.* teach (column 2 bridging column 3; column 3 bridging column 4; column 6, last paragraph; column 9, first paragraph; column 11, lines 1 to lines 54; column 12 bridging column 13; column 19, first paragraph; and columns 43 and 44):

A process for delivery of radiolabeled nucleic acid molecules or radiolabeled peptide

nucleic acid to a cell, which process comprises associating a crown ether to either a nucleic acid polymer or a peptide nucleic acid polymer through a polyamine linker [which is positive charged within its own biochemical structure], mixing the crown ether containing nucleic acid polymer with a polymer carrier, and delivering the crown ether containing nucleic acid polymer complexed with the polymeric polymer to a cell. As a result of the teaching provided by the Hnatowich *et al.* reference, the crown ether based chelator is electrostatically linked to a cDNA by a positive charged linker, *e.g.,* polyamine. Not only that the '861 patent teach complexes of nucleic acid molecules associated with a chelator, the patent on column 19 further teaches that polymeric carriers including polyglycolic acid can be associated or linked to the DNA-chelator complex as controlled release formulation to enhance the delivery of DNA polymer to a target cell.

It would have been obvious for one of ordinary skill in the art to employ any chelator including crown ether bound to polylysine in the conjugate or composition of Kayyem. One of ordinary skill in the art would have been motivated to have employed crown ether as a chelator or polychelator for the purpose of conjugating it covalently to the -NH2 moiety of a cationic polymer such as a polylysine, because Hnatowich teaches that chelator moieties of crown ether are known in the prior art as effective chelators for use in real time monitoring of the delivery of polymers to cells *in vivo.* Further Kayyem *et al.* teach that any of the known paramagnetic metal ion chelators attached covalently to the -NH2 moiety can be used for *in vivo* in gene delivery and/or gene therapy for the purpose of facilitating up take and expression of a DNA.

Thus, the claimed invention as a whole was *prima facie* obvious.

The following prior art is further cited to indicate that modified polylysine comprising a polyether and an active substance is known to enhance the concentration of the substance at a desired target site:

US Pat No. 6,395,254 B1.

Claim Rejections

Rejection, Obviousness Type Double Patenting-No secondary Refence(s)

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 14-26 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 of U. S. Patent No. 6,818,626, filing date January 21, 1999. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-5, 8-17 of the '769 and claims 14-26 of this instant application are all encompass:

A process for delivering a polynucleotide to a cell comprising:

a) forming a complex consisting of a polynucleotide and a chelator, wherein electrostatic interaction of the chelator with one or more components of the complex requires the presence of a metal ion coordinated by the chelator; and

b) delivering the complex to the cell.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant application embraces the invention as set forth and claimed in invention of Patent No. 6,818,626. Thus Patent No. 6,818,626 anticipates the dependent claims of the instant application. For example, claims 6-8 of Patent No. 6544956 are the same invention as claims 6-8 of the instant application. Thus the claimed process for delivery of a polynucleotide of the '626 and this instant application are obvious variants of one another.

Conclusion

No claim is allowed.

Claims Objections

Cross-Referennce to Related Application. The disclosure is objected to because the cross-reference to related application on the first page of the specification required to be updated with the now U. S. Patent No. 6,818,626 corresponding to U.S. application serial No. 09/234,606, filed on Jan 21, 1999.

Any inquiry concerning this communication or earlier communications from the

examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nguyen Dave can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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